Tow-Photon Polymerization (2PP) enables 3D microsystems for Pharmatechnology

E.Taiedinejad[1,2], P. Erfle[1,2], C. Bausch[3], A. Dietzel[1,2]

[1] Technische Universität Braunschweig, Institut für Mikrotechnik; 38124; Braunschweig; Germany; e.taiedinejad@tu-braunschweig.de

[2] Technische Universität Braunschweig, Zentrum für Pharmaverfahrenstechnik- PVZ Franz-Liszt-Straße 35a, 38106 Braunschweig, Germany

[3] Fraunhofer-Institut für Mikrotechnik und Mikrosysteme IMM; Carl-Zeiss-Straße 18-20; 55129 Mainz; Germany

ABSTRACT

Two-photon polymerization(2PP) is a process for three-dimensional (3D) micro-and Nano structuring based on the locally controlled curing of liquid precursors (light-sensitive resins) by photochemical triggered polymerization. In this decade, will be hearing a lot about this technic being applied to pharmaceutical applications like fabricating 3D microchannels for nanoparticle precipitation, nano-porous membranes and scaffolds for cell culturing, biomimetic organ-on-chip systems. This paper presents 2pp applied microsystems for continuously generating lipid nanoparticles which are one of the most important drug carrier system. The most important advantages of 2pp is manufacturing 3D shapes that is not possible with lithographic micro and nano fabrication technologies. Also, it will be shown how 2pp fabricated microchannel can be integrated with continuous size measurement by flowDLS for the feed-back controlled generation of nanoparticles.

Keywords: Two-photon polymerization (2PP), 3D micro structure, pharmaceutical applications

INTRODUCTION

Two-photon polymerization (2PP) is an emerging technology for the manufacturing of 2D, 2.5D and 3D polymer structures with feature sizes from approx. 200 nm to several millimeters. In the laser focus, a sufficiently high intensity of the laser light causes local non-linear absorption and polymerization and thus curing of the coating. The use of a galvo scanner enables the precise control of the laser light in the resist, which allows a step-by-step construction of a complex three-dimensional object. It can be used in manufacturing of micro-mixers with different 3D parts like nozzles for coaxial injection, a sequence of stretch-and-fold elements and inlet filters, and many 3D structures that cannot be realized by conventional 2.5D techniques [1]. As examples Fig 1 shows two different 3D flow focusing micro-mixers that were fabricated with 2PP technics.

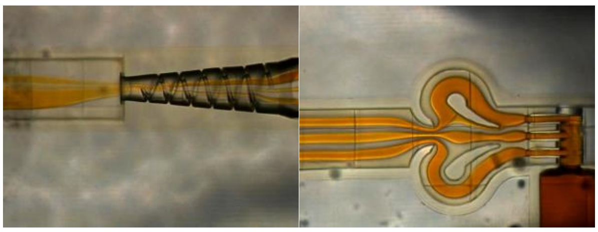

Fig 1. indicates 2 different 3D flow focusing micro-mixers fabricating with 2PP technic.

RESEARCH CONCEPT

With the advent of micro-mixers, another opportunity arose for the bottom up production of lipid nanoparticles as carrier systems or nanoparticle drugs. Lipid in a

https://doi.org/10.24355/dbbs.084-202110261752-0

water-miscible solvent is mixed with an aqueous solution and particles of less than 100 nm and narrow size distributions precipitate. A further advantage of microfluidic low-energy processing is that high temperatures, high shear stresses, high pressures and product contamination due to mill erosion which can cause damage to the active ingredients are avoided [2]. But still, the biggest obstacle is fouling by deposition of lipid on the channel walls, leading to a higher nanoparticle polydispersitye and even channel blocking [3]. Recently, a coaxial lamination mixer (CLM) enabled by 2PP was introduced to completely eliminate contact of the organic phase with the channel walls while efficiently mixing organic and aqueous [1].

A very unique application of 2PP fabricated micro-channels is the combination of controllable microfluidic nanoparticle generation with dynamic light scattering (DLS) for particle size analysis [6]. The system envisaged is a feedback-regulated nanoparticle reactor is to be realized with which the size, size distribution and shape of the manufactured particles can be precisely adjusted and a long-term stable process ensured. This is the aim of a cooperation project between Institute for Microtechnology (IMT) at the TU Braunschweig with the flowDLS developed at the Fraunhofer Institute for Microtechnology and Microsystems (IMM) in Mainz. The necessary verification of particle properties by measurement and counting has so far only been possible within a separate analytical system after preparation is completed. The evaluation of the nanoparticles in a collected sample provides only statements about a sample produced within a longer period of time and does not open any possibilities to constantly influence the precipitation process in the micro mixers or the emulsifying systems as this is only possible by in-situ measurement in the channels.

Fig. 2 shows the important parts of the flowDLS system including a laser, a detector for the scattered light and the transparent 3D micromixer for generating nanoparticles fabricated with 2PP technology. Laser light can shine through an optical aperture into the channel and the scattered light can give information about the particle size and morphologies.

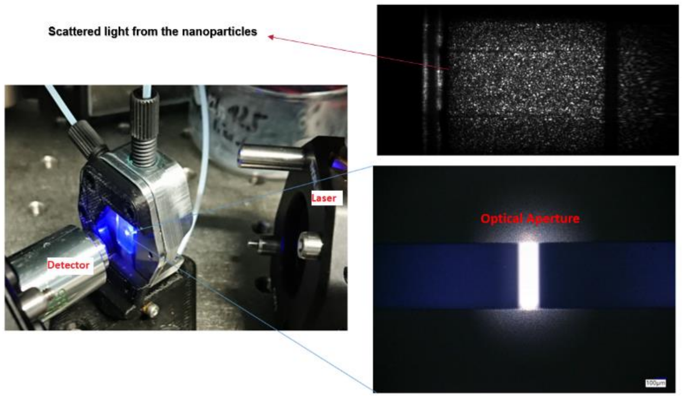

Fig 2- *The FlowDLS system for online and continuous measurement of generated nanoparticle inside the microfluidic channels.*

CONCLUSIONS

2pp can open a window of new opportunities to pharmaceutical engineering in fields where processes in micro and nano devices can be used beneficially. This technique enables fabrication of very complicated 3D designs and shapes with different non-toxic and even biocompatible polymers. An example is given by the microfluidic precipitation device that can be integrated with flowDLS nanoparticle measurement for feedback controlled nanoparticle production.

ACKNOWLEDGEMENT

This work is supported by the Deutsche Forscghungsgemeinschaft in the frame of the project ´´Detected (DLS feedback controlled Continuous particle production) ´´. This work is carried out within the Detected project between Technical Universität Braunschweig and Fraunhofer-Institut für Mikrotechnik und Mikrosysteme (IMM).

https://doi.org/10.24355/dbbs.084-202110261752-0

REFERENCES

1 Erfle, Peer, Riewe, Juliane, Bunjes, Heike, and Dietzel, Andreas, ‘Goodbye fouling: a unique coaxial lamination mixer (CLM) enabled by two-photon polymerization for the stable production of monodisperse drug carrier nanoparticles ‘, Lab on a chip, 21/11 (2021) 2178-2193

2- Sinha, Biswadip; Müller, Rainer H.; Möschwitzer, Jan P. (2013): Bottom-up approaches for preparing drug nanocrystals. Formulations and factors affecting particle size. ln: *International Journal of Pharmaceutics* 453 (1), S. 126-141. DOI: 10.1 016/j.ijpharm.2013.01.019

3- Dietzel, Andreas (Ed.) (2016): Microsystems for pharmatechnology: Manipulation of fluids, particles, droplets, and cells. Springer, Cham. ISBN 978-3-319-26920-7

4- Erfle, Peer; Riewe, Juliane; Bunjes, Heike; Dietzel, Andreas (2017): Optically monitared segmented flow for controlled ultra-fast mixing and nanoparticle precipitation. ln: *Microfluidics and Nanofluidics* 21 (12), S. 1089. DOI: 10.1007/s10404-017-2016-2.

5- Liu, Lili; Cai, Xiaoshu; Zhang, Jie; Xu, Chengze (2015): Particle-size Measurements in a Microchannel with Image Dynamic Light Scattering Method. ln: *Procedia Engineering* 102, S. 904-910. DOI: 10.1 016/j.proeng.2015.01.211.

6- Destremaut, Fanny; Salmon, Jean-Baptiste; Qi, Ling; Chapel, Jean-Paul (2009): Microfluidics with on-line dynamic light scattering for size measurements. In: Lab on a chip 9 (22), S. 3289–3296. DOI: 10.1039/b906514h.

https://doi.org/10.24355/dbbs.084-202110261752-0